REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the foregoing amendment and following remarks are respectfully requested. Claims 10-16 and 41-76 are currently pending. Claims 10-16, 41, 48 and 49 have been allowed. Claims 42-47 and 50-76 remain at issue. This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the required fee.

In paragraph 5 of the official action, the examiner asserted that the oath/declaration was defective allegedly for containing non-initialed and/or non-dated alterations. The applicants hereby submit a newly executed oath/declaration from the inventors, Dr. Huan Li and Dr.Vassilios Papadopoulos. In view of the foregoing, withdrawal of the objection is respectfully requested.

In paragraph 6 of the official action, the examiner objected to the word "detectable" in claim 51 and suggested replacing this word with the word "detectably." The applicants have adopted the examiner's suggestion for claim 51 and hereby respectfully request withdrawal of the objection.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 42-47 and 53-76

In paragraph 7 of the official action, the examiner rejected claims 42-47 and 53-76 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification to enable one skilled in the art to make or use the invention. Specifically, the examiner stated that while the specification is enabling for an isolated nucleic acid comprising a nucleotide sequence as set forth in SEQ ID NO: 2 or an isolated nucleotide sequence that encodes a fragment of the polypeptide as set forth in SEQ ID NO: 7, wherein the polypeptide fragment is capable of regulating progesterone biosynthesis, the specification

does not reasonably provide enablement for an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable of binding to a peripheral-type benzodiazepine receptor (PBR), that is capable of regulating steroid biosynthesis, or is capable of mediating cholesterol delivery. The examiner further asserted the specification is not enabling for an isolated nucleic acid that encodes a polypeptide that is capable of binding a PBR receptor, regulating steroid biosynthesis, or mediating cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41. The examiner alleged that despite the general guidance as to what amino acid positions could be potentially altered, the specification fails to teach the skilled artisan how to use or make the biologically active PAP7 variants without resorting to undue experimentation to determine the specific biological activities of the variants. The examiner further asserted that while the specification teaches that full length PAP7 increases progesterone biosynthesis while partial PAP7 decreases the level of progesterone biosynthesis, the specification does not teach any methods or working examples that indicate full length PAP7 or any PAP7 fragments are able to regulate the biosynthesis of steroids other than progesterone or mediate cholesterol delivery.

Amended claims 43 and 44 are directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is either capable of regulating progesterone biosynthesis or impairing cholesterol delivery. Amended claims 45-47 are directed to an isolated nucleic acid that encodes a polypeptide that is either capable of regulating progesterone biosynthesis or impairing cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41(a) or 41(b) under the following stringent conditions: a final wash in 0.1X SSC at 65°C. As stated above, the examiner has acknowledged that the presently claimed variants and hybridizing nucleic acids that encode a polypeptide capable of regulating progesterone biosynthesis and impairing cholesterol delivery is enabled by the specification (see official action, *e.g.*, page 6, line 18 to page 7, line 5; advisory action; page 4, lines 4-8 of the specificatioin).

The applicants submit the specification fully enables one of skill to identify PAP7 variant or hybridizing nucleic acids of claims 42, 44, 45, and 47 having the biological activity of impairing cholesterol delivery of claims 42, 44, 45, and 47. Specifically, the specification teaches methods for identifying DNA fragments encoding PAP7 (see page 7, lines 1-8; page

14, line 33 to page 15, line 5) wherein PBR binds PAP7 or wherein cholesterol transport into a cell is impaired (see page 8, lines 10-16). These methods allow for identification of fragments that can be used as antagonist to inhibit the PAP7-PBR association and thus reduce or inhibit PBR activity (see page 34, lines 24-30) as well as modulate cholesterol transport (see page 34, lines 24-34; page 35, lines 25 to page 36, line 1).

In fact, the applicants submit data herewith that demonstrates what was already taught by the specification for both the biological activities of impairing cholestrol transport and binding PBR by PAP7. For example, the same PAP7 vector construct pSVPAP7p (which contains the C-terminal PAP7 fragment 228-445), which demonstrated that a partial PAP7 fragment decreased the level of progesterone biosynthesis in Example 5, also inhibited pregnenolone formation in the inner mitochondrial membrane of MA-10 Leydig cells (see Appendix A Li *et al., Molecular Endocrinology* 15:2211-2228, 2219 second column (2001)). Inhibition of pregnenolone formation is due to a decrease accumulation of cholesterol at the inner mitochondrial membrane and thus reflects PAP7's ability to impair cholesterol transport (see Li *et al.* at pg. 2219 and Figure 10).

The biological ability of PAP7 to directly bind PBR is full enabled by the applicants disclosure as well. For example, PBR binding domains as well as other important regions of PAP7 (SEQ ID NOS: 2 and 7) were identified by the applicants on page 16, line 27 to page 17, line 5 (see also page 49, line 10 to 34). The applicants were again able to demonstrate PBR binding domains of PAP7 indeed interact with PBR using a GST (glutathione-S-transferase)-PAP7 (amino acids 216-445) fusion protein. Figure 3(D) of Li *et al.*(pages 2214 second column and page 2215) demonstrate PAP7 binding to PBR.

The applicants respectfully submit not every biological activity is required to be discussed in a separate working example of the specification. In fact, the enablement requirement simply requires the disclosure, when filed, to contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. In this case, the specification discloses that methods well known in the art can be used to characterize the claimed biological activities (impair cholesterol transport) of PAP7. The specification also identifies particular regions of PAP7 that can be modulated to study the binding of PBR (page 16, lines 27 to page 17, line 5 and page 49, lines 10 to 34). Furthermore, the specification states that combining the facts that

PBR (1) is hydrophobic protein, (2) impairs cholesterol delivery from the outer to the inner mitochondrial membrane, (3) binds Acyl-CoA binding proteins, and (4) is a functional component of the steroidogenic machinery (see pg. 2, lines 3-22 and pg. 49, lines 10-33), with the facts that PAP7 (4) contains an Acyl-CoA binding signature region, (5) contains fatty acylation (myristoylation) sites, and (6) regulates progesterone production, which is index for steroid biosynthesis, which in turn requires cholesterol, PAP7 binds PBR and impairs cholesterol transport (see pg. 49, lines 10-33, Example 5). These findings were verified in the later published Li *et al.* article.

Nevertheless, solely for the purpose of expediting prosecution, and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have canceled claims 42, 45, 53-56, and 65-68. Accordingly, in view of the structural and functional information regarding the claimed nucleic acids of claims 44 and 47, along with the later verified results in Li *et al.*, the applicants submit these claims are supported by an enabling disclosure.

Claims 57-64, and 69-76 ultimately depend upon claims 43, 44, 46, and 47 (*e.g.*, vectors comprising such a nucleic acid, host cells comprising such vectors, process for producing protein encoding by such nucleic acid, reagent comprising such a nucleic acid) and are therefore also enabled by the specification. In view of the foregoing amendments and remarks, the applicants submit that the rejection of claims 45-47 and 53-76 pursuant to 35 U.S.C. §112, first paragraph, for lack of enablement, is overcome and should be withdrawn.

Claims 50-52

In paragraph 8 of the official action, the examiner rejected claims 50-52 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the examiner alleged that the specification does not disclose a correlation between a specific disease state and an alteration in expression level, form, temporal pattern, of the PAP7 nucleic acid sequence of SEQ ID NO: 2. The examiner further asserted significant further experimentation would be required of the skilled artisan to identify individuals with a disease involving the PAP7 nucleic acid molecule of SEQ ID NO: 2.

Amended claim 50 is directed to a reagent comprising a nucleic acid of claim 41, wherein the nucleic acid is detectable labeled. Amended claim 51 is directed to a reagent comprising a single-stranded nucleic acid of claim 41, wherein the nucleic acid is complementary and is detectably labeled. Amended claim 52 is directed to a reagent comprising a single-stranded nucleic acid of claim 41, wherein the nucleic acid amplifies peripheral-type benzodiazepine-receptor-associated protein-7 (PAP7) sequences. As suggested by the examiner, the applicants have removed the word "diagnostic" from these claims in order to overcome the enablement rejection. Similarly, the applicants have removed the word "diagnostic" from claims 60, 64, 72, and 76. In view of the foregoing amendments, the applicants respectfully submit the rejection of claims 50-52 to 35 U.S.C. §112, first paragraph, for lack of enablement, has been overcome and should be withdrawn and a rejection of amended claims 60, 64, 72, and 76 on the same grounds would be improper.

Rejections Under 35 U.S.C. §112, First Paragraph, Written Description

In paragraph 9 of the official action, claims 42-47 and 53-76 under 35 U.S.C. §112, first paragraph, were rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The examiner asserted that while the specification described an isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO: 2 and an isolated nucleic acid molecule which encodes a fragment of the polypeptide as set forth in SEQ ID NO: 7 that is capable of regulating progesterone biosynthesis, the specification does not teach any significant or functional characteristics (mediation of cholesterol or PBR binding) of all possible PAP7 polynucleotide sequences that are 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 or the hybridizing polynucleotides to the nucleic acid sequence of SEQ ID NO: 2. The examiner alleged that the fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines since Example 14 discusses protein variants with a specific activity disclosed in the specification.

The applicants respectfully submit that the presently claimed variants and hybridizing nucleic acids that encode a polypeptide capable of regulating progesterone biosynthesis is

fully described by the specification (claims 43, 46, 57-60, 72-75) (see official action, *e.g.*, page 6, line 18 to page 7, line 5). With regard to examiner's comments regarding the Written Description Guidelines, the applicants respectfully submit the specific biological activities of PAP7 to bind to PBR and impair cholesterol delivery are described in the specification and are to be correlated with the claimed variant and hybridizing nucleic acids. Specifically, the specification requires its 90% variants to exhibit activity similar to the activity of the PAP7 protein (see page 18, lines 15-27). The specification also provides for the stringent hybridization wash conditions on page 17, lines 6-18. The biological activity of PAP7 binding of PBR is discussed throughout the specification, for example, on page 34, lines 14 and 15; page 49, lines 30-35; page 50, lines 12-17; and page 19, lines 19-21. For example, the disclosure teaches that due to the progesterone studies in Example 5, it is believed that PAP7 binds to PBR and a fragment of PAP7 would act as a competitor of the native PAP7 (see page 51, lines 10-26). As discussed above, Li *et al.* demonstrates PAP7 directly binds to PBR (see Figure 3(D) and (E) and page 2214 second column of Li *et al.*).

The biological activity of impairing cholesterol delivery is discussed throughout the specification (page 2, lines 6-11; page 34, lines 21-34; page 35, line 25 to page 36, line 10; page 49, lines 10-22; and page 51, lines 27 to page 52, line 5) and is acknowledged by the examiner (see advisory action, last paragraph). For example, the disclosure teaches that PAP7's sequence motif is hydrophobic and similar to outer proteins associated with the outer mitochondrial membrane. The applicants stated these properties could enable PAP7 to pass hormone stimulation signal to and interact with PBR thus regulating PBR activity in cholesterol transport (see pg. 49, lines 10-22). In fact, the vector pSVPAP7p used in the progesterone studies of Example 5 was show to inhibit cholesterol transport in later published works of the applicants (see Li *et al.*, pg. 2219, second column and Figure 10). The applicants respectfully submit the specification not only describes the specific PAP biological activities of progesterone regulation, cholesterol transport impairment, and PBR binding, which are all required for its claimed variant and hybridization nucleic acids, but also demonstrate these specific activities either directly in the specification (see Examples 1 and 5) or in the later published results of Li *et al.* Accordingly, the applicants respectfully submit the instant application is analagous to Examples 9 and 14 of the Revised Interim Written Description Guidelines since the specific activity of PBR binding and cholesterol transport

mediation is sufficiently disclosed in the application and this activity is required in the variant nucleic acid claims.

Nevertheless, as discussed above, claims 42, 45, 53-56, and 65-68 have been canceled without prejudice. Claims 57-64 and 69-76 ultimately depend upon claims 43, 44, 46, and 47 (*e.g.*, vectors comprising such a nucleic acid, host cells comprising such vectors, process for producing protein encoding by such nucleic acid, reagent comprising such a nucleic acid) and are therefore also enabled by the specification. In view of the foregoing amendments and remarks, the applicants submit that the rejection of claims 45-47 and 53-76 pursuant to 35 U.S.C. §112, first paragraph, for lack of enablement, is overcome and should be withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

In paragraph 11 of the official action, the examiner rejected claims 45-47 and 65-76 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Specifically, the examiner alleged that it is unclear how the isolated nucleic acids hybridize to the complement of the complement recited in claim 41(c).

Amended claims 46 and 47 are now directed to an isolated nucleic acid that encodes a polypeptide that is capable of regulating progesterone biosynthesis, or impairing cholesterol delivery and hybridizing to the complement of the nucleic acid of claim 41(a) or 41(b) under the following stringent conditions: a final wash in 0.1X SSC at 65°C. As suggested by the examiner, the nucleic acids of claims 46 and 47 will hybridize to the complement of the nucleic acid of claim 41(a) or 41(b).

As discussed above, claims 69-76 ultimately depend upon either claims 46, or 47 (*e.g.*, vectors comprising such a nucleic acid, host cells comprising such vectors, process for producing protein encoded by such nucleic acid, reagent comprising such a nucleic acid) and are therefore no longer indefinite. In view of the foregoing amendments and remarks, the applicants submit that the rejection of claims 45-47 and 65-76 pursuant to 35 U.S.C. §112, second paragraph, for indefiniteness, is overcome and should be withdrawn.

CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
PILLSBURY WINTHROP LLP

By: _____

Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40944
Tel. No. (703) 905-2144
Fax No. (703) 905-2500

TAC/PAJ
P.O. Box 10500
McLean, VA 22102
(703) 905-2000